REMARKS

Reconsideration of the this case is respectfully requested. Claims 1-6 and 10-72 are currently pending. No claims have been amended herein. No claims are canceled herein.

WITHDRAWAL FROM ISSUE

It should be respectfully noted that the Applicants maintain the position that, according to the Administrative Procedure Act, 5 U.S.C. § 701 *et seq.*, established law does not allow for withdrawal of an application by the PTO after the issue fee has been paid as is the case with the instant application. More to the point, Applicants point out that any authority to withdraw a duly allowed application is exceeded if PTO authorities have exceeded their authority by acting in any arbitrary or capricious matter. Blacklight Power, Inc. v. Rogan, 295 F.3d 1269, 63 USPQ2d 1534 (Fed. Cir. 2002).

Applicants also point out that 35 U.S.C. §151 compels the issuance of an application when the issue fee has been paid, as in the present case:

> 35 U.S.C. §151.
>
> If it appears that applicant is entitled to a patent under the law, a written notice of allowance of the application shall be given or mailed to the applicant. The notice shall specify a sum, constituting the issue fee or a portion thereof, which shall be paid within three months thereafter.
>
> Upon payment of this sum the patent shall issue, but if payment is not timely made, the application shall be regarded as abandoned.

Therefore, it is Applicant's position that § 151 does not allow for withdrawal of an application by the PTO after the issue fee has been paid. That in so doing, the PTO has respectfully acted in an arbitrary manner and PTO officials have exceeded their authority in withdrawing the '117 application from issue. Reconsideration is requested.

However, Applicants duly note that the Supreme Court has observed that agency actions are entitled to judicial respect when they are reasonably taken and in accordance with the

specialized experience of agency officials. Skidmore v. Swift & Co., 323 U.S.134, 139-40 (1944). Therefore, Applicants hope to redress any misunderstandings and work with the Examiner and the PTO to resolve any outstanding difficulties associated with issuing this case in a timely and efficient manner.

ADDITIONAL FILINGS

In addition, Applicants respectfully retain their right to file a divisional and/or continuation application covering the withdrawn invention as necessary to protect their proprietary interests in the filed invention.

ORIGINAL SPECIFICATION IN SUPPORT OF THE CLAIMS AS AMENDED

1. WITH REGARDS TO THE QUESTION OF PARTICLES GREATER THAN 0.1UM:

GTC uses membranes to separate particles from small molecules in a milk feedstream; these particles are greater than 0.1 um (such as, fat globules, casein micelles, and cells). The membrane is used to perform a separation between unwanted contaminants and the valuable transgenic proteins expressed in the milk. Each of these unwanted particles are well-known components of milk and their size is well documented. (see attached citations).

Fat globules –	0.1 – 20um
Casein micelles -	0.05 – 0.6um
Cells -	10 – 100um

Milk is clearly embodied in the patent application and may be found as a reference in claim 8 of the original application, as well as various other supports in the specification.

Application References: [All from Original Specification: para. 4, page 2; para 14, p. 6; para 17, p. 6; para 18, p. 6; Fig. 5; Fig. 9 etc.].

The membrane used for the removal of these milk particles according to the invention, and consequently providing the limits of filtration size as recited in the claims, is from the methods section of the specification. The unit used by the inventors was a filter that was ceramic based and had a nominal pore size of 0.2um. A 0.2um microporous membrane will retain particles in the "micron" range from 0.1um to 10 um. The membrane used for the clarification experiments were indeed used to separate these particles from the desired product. Specific references to the membrane used may be found in the materials and methods section of the application, and is therefore implicit in the data provided. **Application References:** [All from Original Specification: page 10 – Definition of Clarification; para 42, p. 13 – recitation of Clarification steps; Fig. 1; para 45, p. 15 – Milk as feedstream with what that means in terms of particle size to those working in the field; para 71, p. 21 ceramic filter pore size; para 74, p. 22; para 78, p. 24; para 81, p. 25 – membrane pore size]. (see also, attached citations reflecting information in the field).

2. SUPPORT FROM SPECIFICATION FOR LATEST AMENDMENTS AND OPERATING RANGE

The experimental microfiltration data found in the original patent application was used to support the unique nature of the invention. The data was organized into a series of graphs and used to determine the ideal operating conditions of a microfiltration membrane. These conditions were then used for the separation of milk components from the transgenic protein expressed in milk. The data shows the optimal cross-flow rate, operating temperature, concentration factor, and the transmembrane pressure (TMP) for the separation. Most importantly, the TMP was found to be optimal at approximately 15psig for the process described. Unfortunately, when the data was presented in this manner it did not clearly demonstrate the differences in operating conditions between the ones used by Van Reis and GTC. This was because the inventors presented their data on graphs in one way and van Reis another. When, in the Amendment after Final the same data from the instant invention was plotted again in a manner consistent with the methods of van Reis the differences between the existing patents of van Reis and the GTC invention became clear. All data as represented in the amended claims is from the original application, citations to support the operation of the instant invention above 100% transition

point flux parameters can be found in the application as filed, and does not constitute new matter.

Application References: [All from Original Specification: para 87, p. 28 – Optimal Parameters – *above* van Reis; Graphs E and F p. 30; para 79, p. 24 – where the current invention "operates"; para 105, p. 42 optimum flow velocity – above van Reis; para 90, p. 32 – where the current invention TMP "must" be run above van Reis' parameters; para 105, p. 42 – optimal flux of IgG1; Chart. Page 36 – optimal operating parameters in a different region of the comparative curve relative to van Reis; para 117, p. 48 directing how to adjust the parameters of the invention in the region in 100% of van Reis]. (see also, attached citations reflecting information in the field).

Graph B and F show the relationship between transmembrane pressure (TMP) and Mass Flux (GMH), a measure of liquid flux and productivity. When simplifying this graph, productivity was not graphed simultaneously, leaving TMP and liquid flux (LMH). Example 1 and 3 in the response section shows the original data from the patent application in this simplified manner. Here the transition point can be easily seen at 7 psig for figure 1 and 10 psig for figure 3. The conclusion which may be made from this information is that the original application, and the amended claims, show optimal transmembrane pressure above the transition point of the curve – above 100%. This is an important piece of information as it further differentiates GTC's invention from the cited prior art.

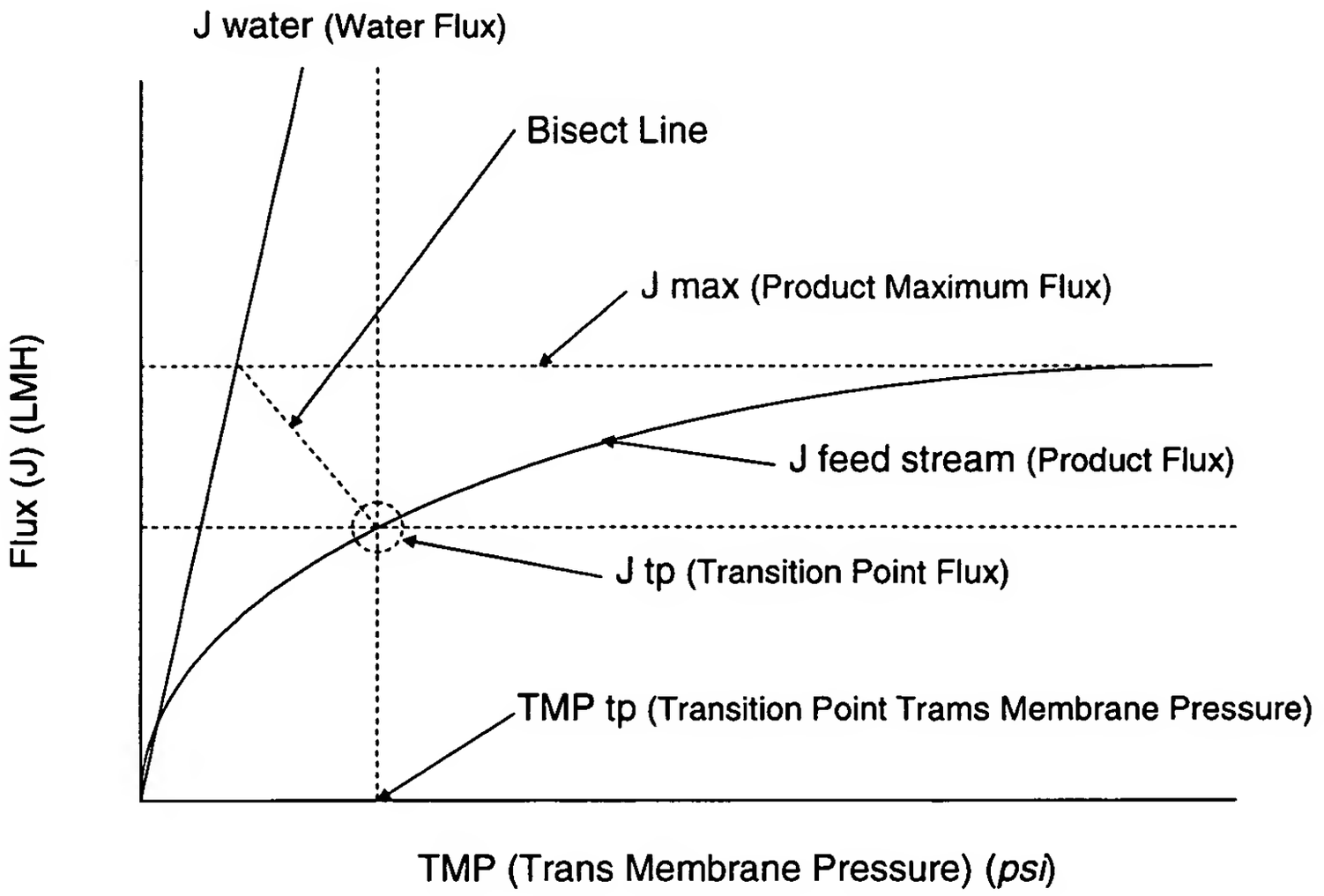
PRIOR RESPONSE AND NEW MATTER

It must be noted at the outset that the existing independent claim (claim 1) was substantially amended previously to address a variety of the Examiner's prior art concerns and to better explain the operating parameters of the current invention. These same amendments also serve to demonstrate that the current application simply operates in a different region and with different capabilities than those provided by the teachings of van Reis as provided in light of Kondo and/or Kunihau. That is what is presented previously and is briefly recreated below. As pointed out above, all of the data used in the last Amendment After Final was data found and presented in the original specification as filed. The primary differences were in the nature of the presentation of the data, not the data itself. Essentially van Reis presented his data and data curves in one way, and the current inventors presented theirs in another. The Amendment After

Final filed by the Applicants and entered by the Examiner functioned to demonstrate what Applicants data, teachings and invention looked like as compared to van Reis (the primary prior art) when plotted on the same data curves. It essentially gives a representation of where van Reis "operates" and where the current invention "operates." This then forms the basis of respectfully saying why van Reis and the current invention are definitively different.

That is the data presented below (originally presented in this form in the Amendment After Final), and compared to van Reis data demonstrates that the current claims and invention are not only not anticipated by van Reis, Kondo and/or Kunihau but that they teach against the current invention. As previously stated Applicants will provide such Declarations from the Inventors for the examples/data points presented, the short response time for this action did not allow these to be generated. Raw data and notebooks will also be provided on request.

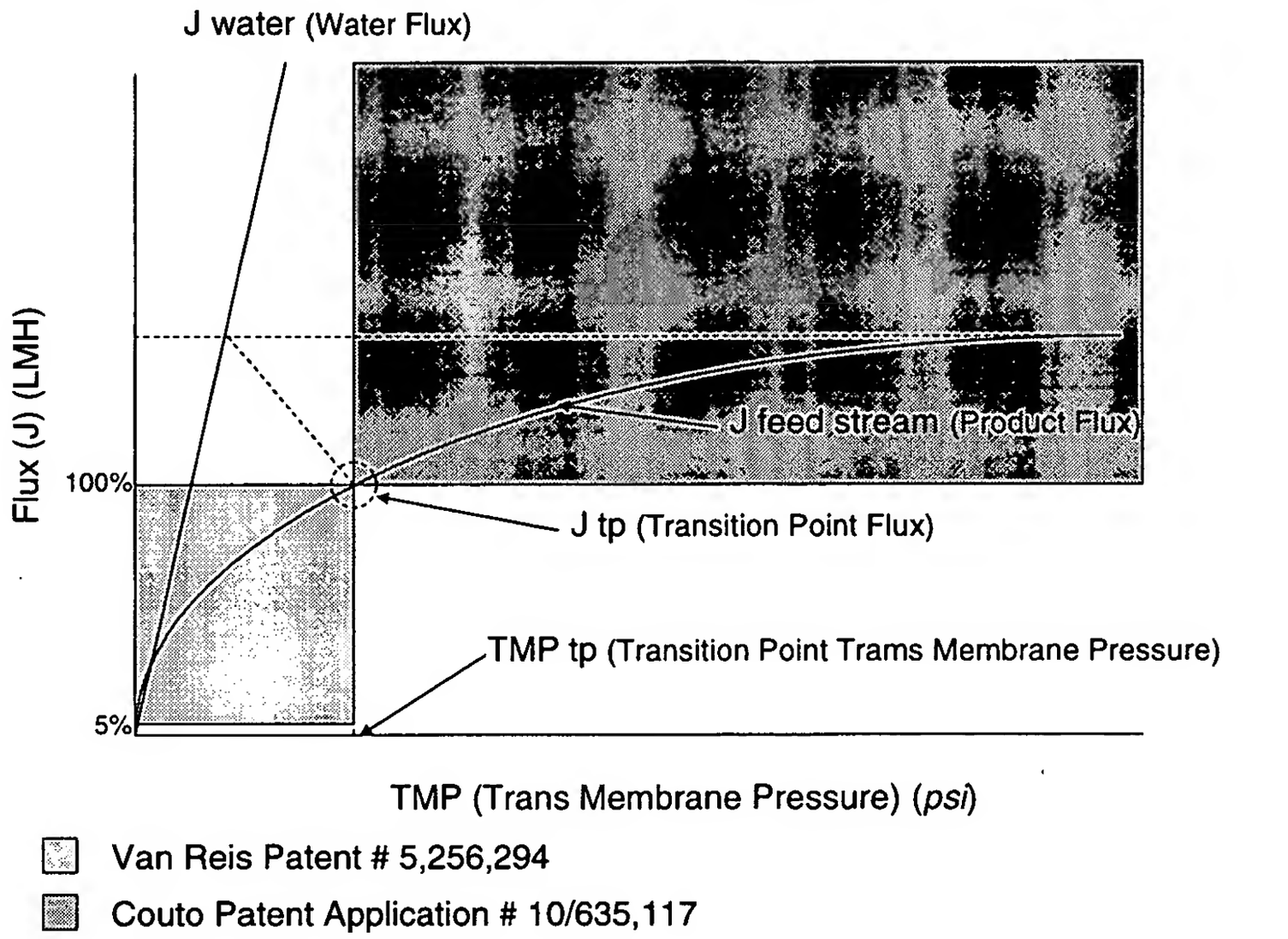
"Diagram # A



In Diagram # A, some of the terms for Claim # 1 of the patent application are defined. With in a TMP vs. Flux graph, two major lines are draws: the Water Flux (J water) and the Product Flux (J feed stream). The Product Flux curve defines a maximum product flux (J max) which intersects the water flux line. At this point a bisecting line is drawn from the intersection of the two lines (J water and J max) to the Product Flux curve. The point at which the bisect

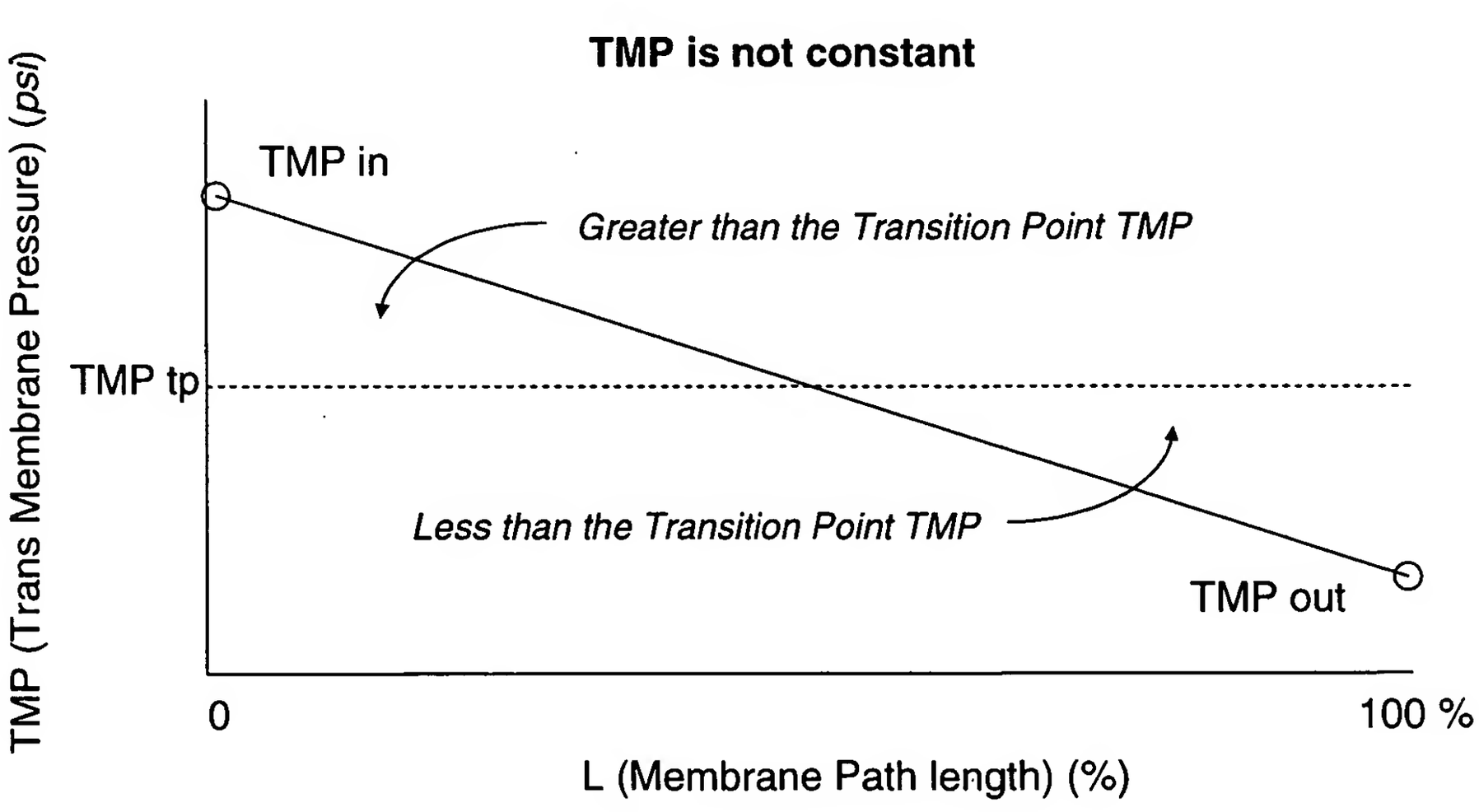
intersects the J feed stream curve is defined as the transition point flux (J tp). A line is dropped directly down to the X axis to define the transition point transmembrane pressure (TMP tp).

Diagram # B



In the Van Ries patent # 5,256,294, the zone that is in claim #1 is the area in light blue in Diagram #B bound by 100% to 5% of the Jtp and the TMP tp vertical line. The current invention rests its amended claims in the area of Diagram #B in light green bound by a Flux greater than 100% of the Jtp and the TMP tp vertical line. Please note Examples #1 to 10 attached.

Diagram # C

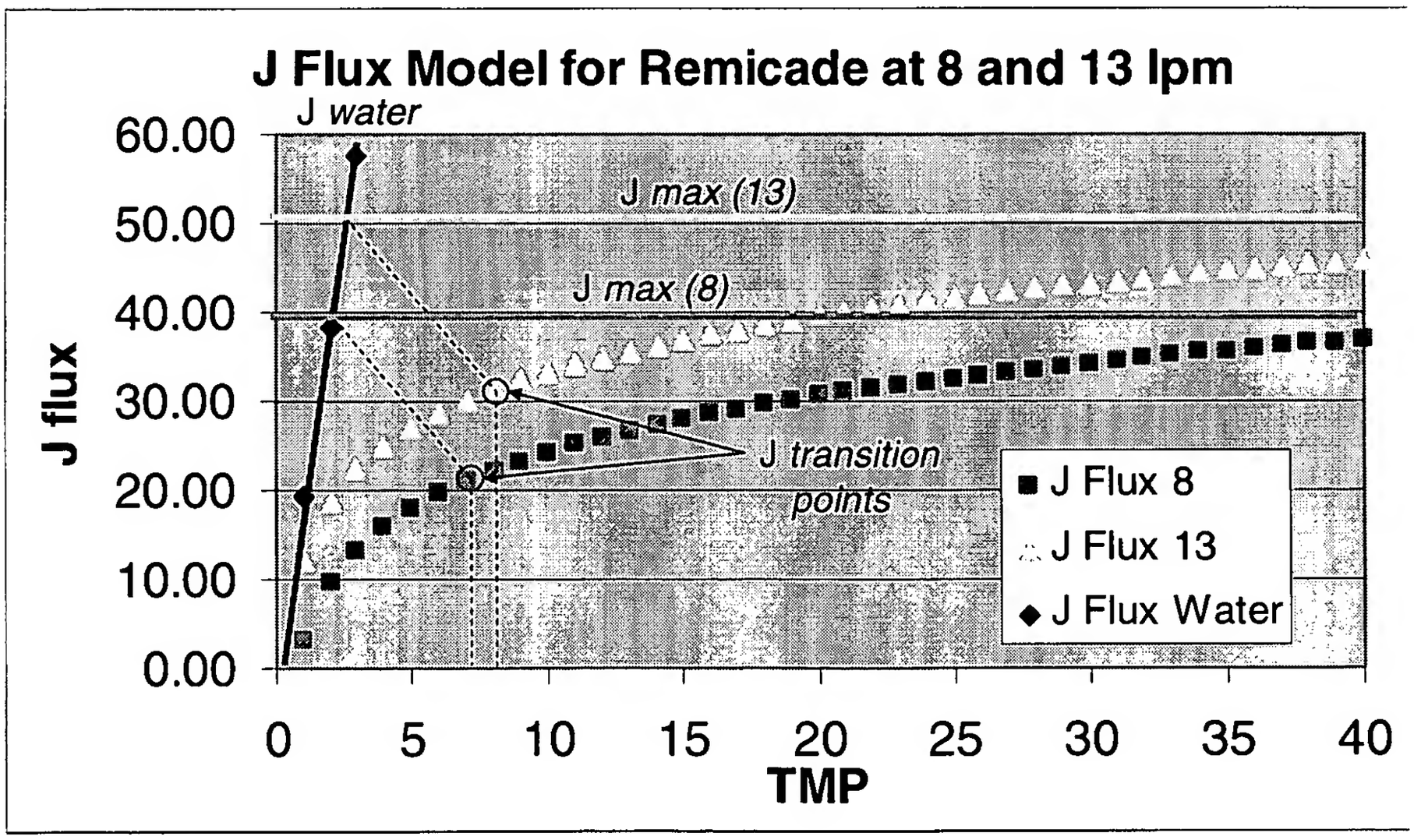


In Diagram # C, additional terms for Claim #1 of the patent application are defined as per the specification. With in a Membrane path length vs. TMP graph, a major line is draws from the membrane inlet TMP (TMP in) to membrane outlet TMP (TMP out). We previously defined on Diagram # A, a point of the X axis as the transition point transmembrane pressure (TMP tp). In claim # 1 of the Van Reis '294 the TMP is stated to be substantially constant and at a level no greater than the TMP tp vertical line. Respectfully, the instant patent application denotes the parameters in Diagram # C that are not constant and include TMPs at a level greater than the TMP tp vertical line. This data can also be illustrated in Diagram # D.

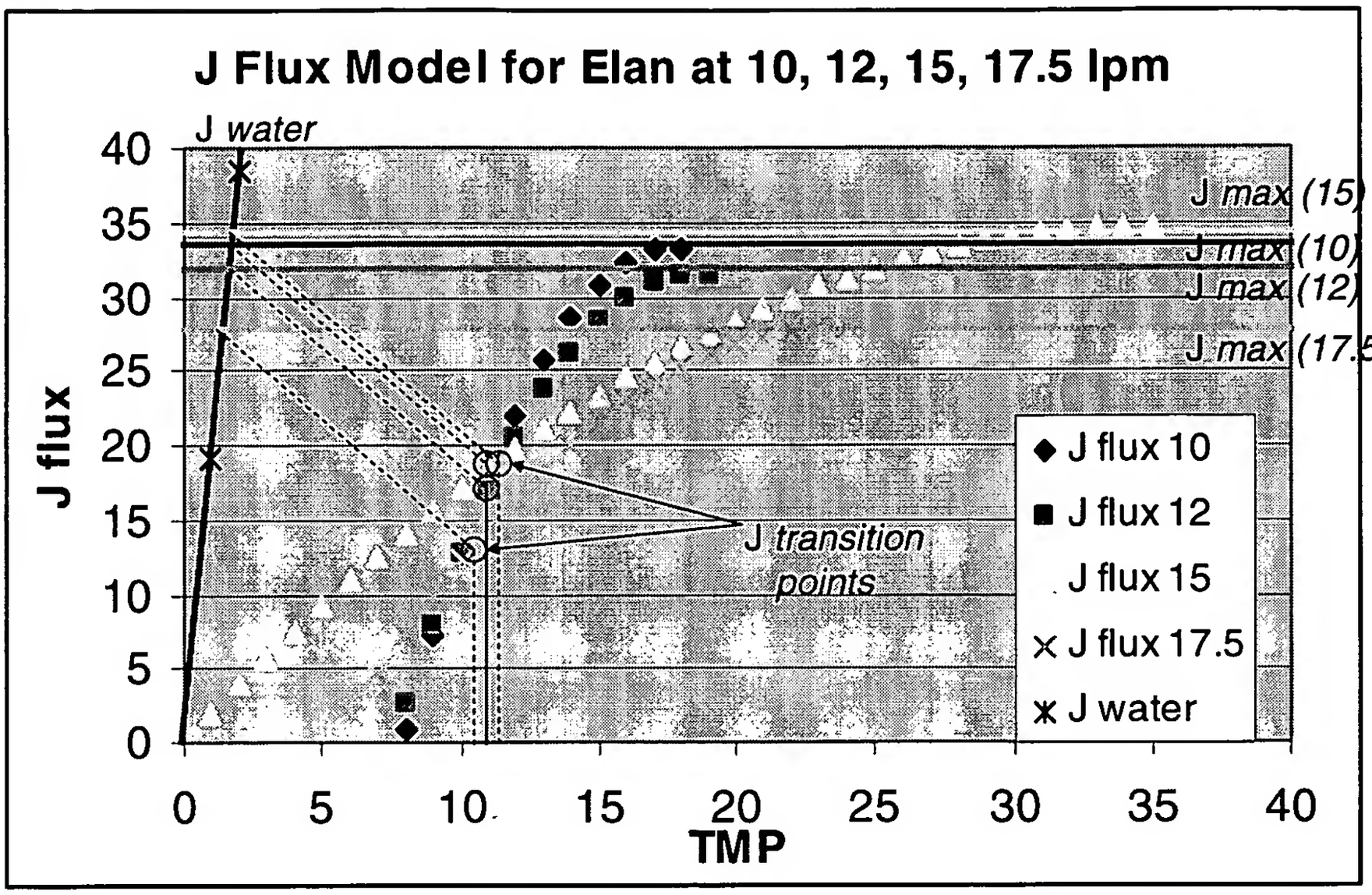
Diagram # D

Run Number	Average TMP Inlet (psi)	Average TMP Outlet (psi)	TMP Transition Point (psi)
1	8.43	-2.43	3
2	2.64	-0.92	1.5
3	5.66	1.93	0.58
4	4.58	0.01	3
5	3.76	2.23	1.5
6	4.92	0.75	1.5
7	4.42	1.93	2.5
8	5.17	0.83	4

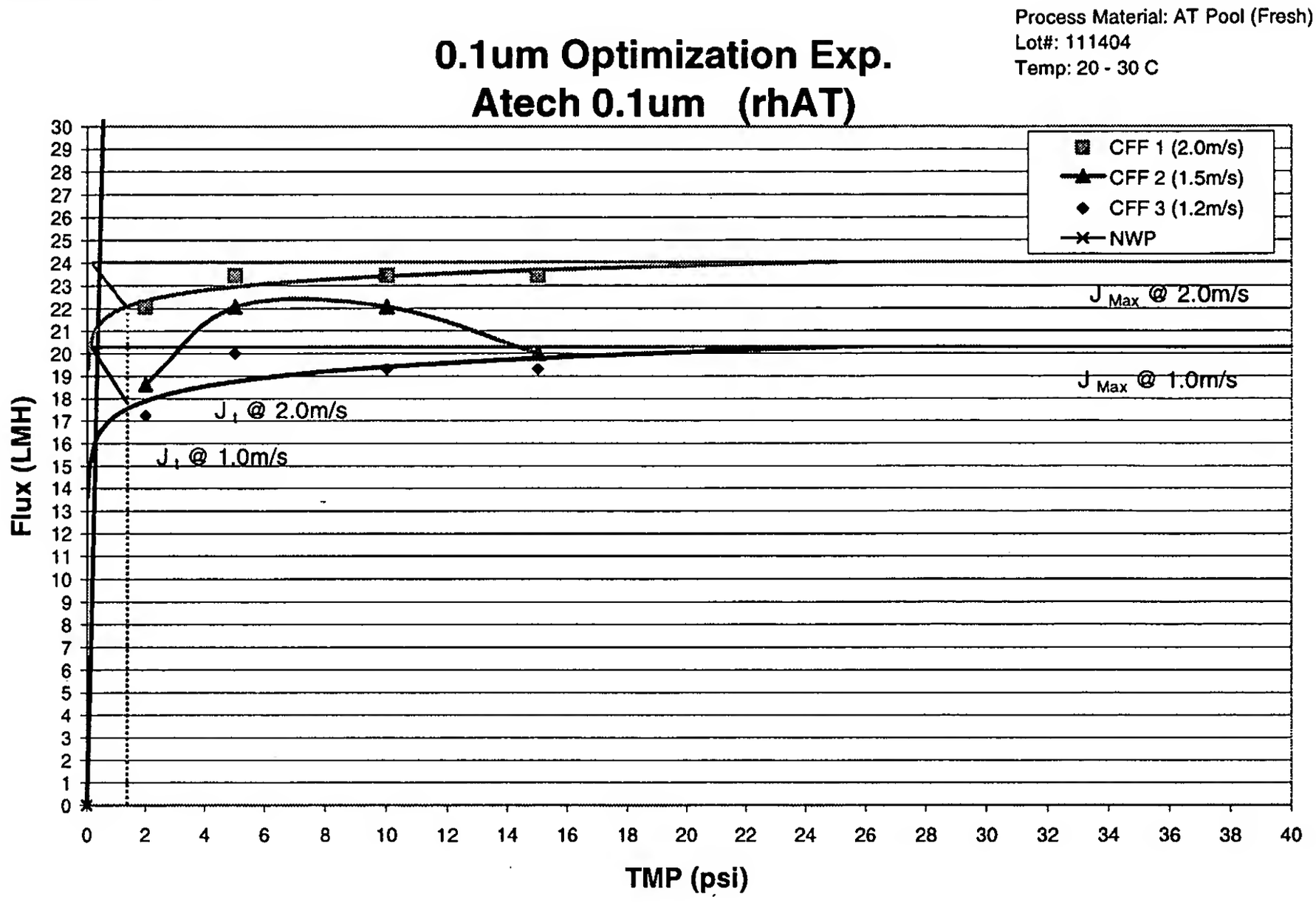
Example #1



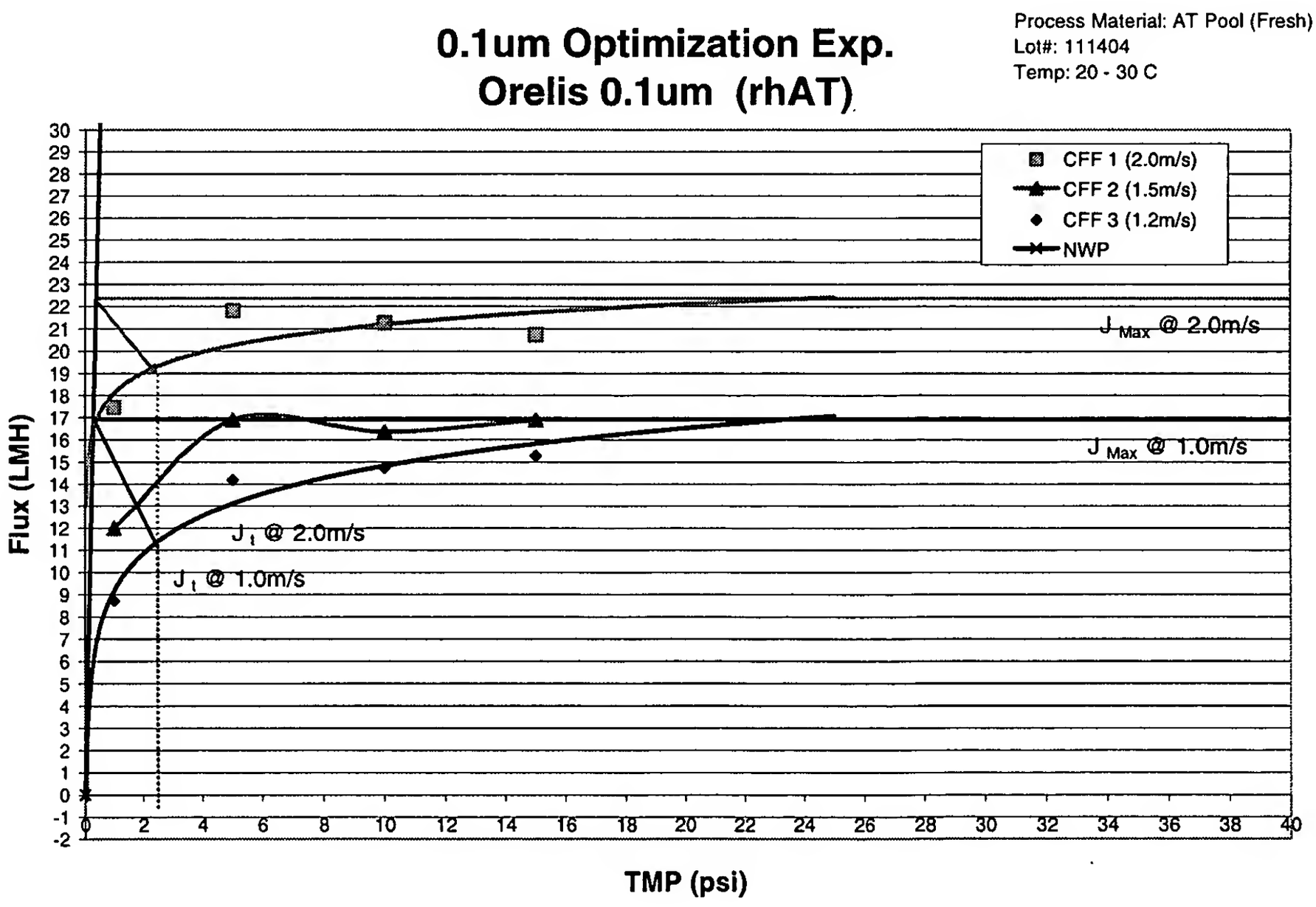
Example #2



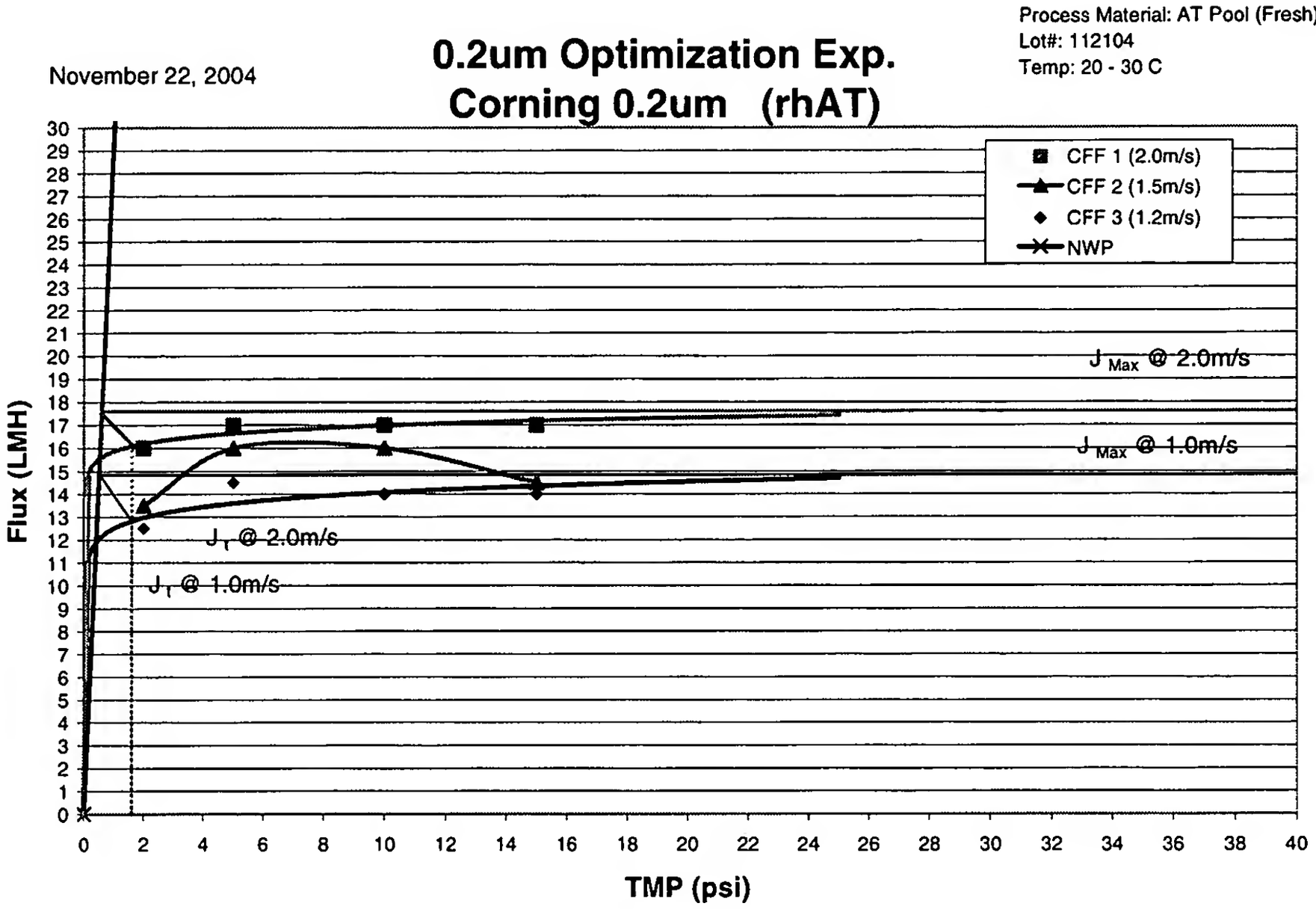
Example #3



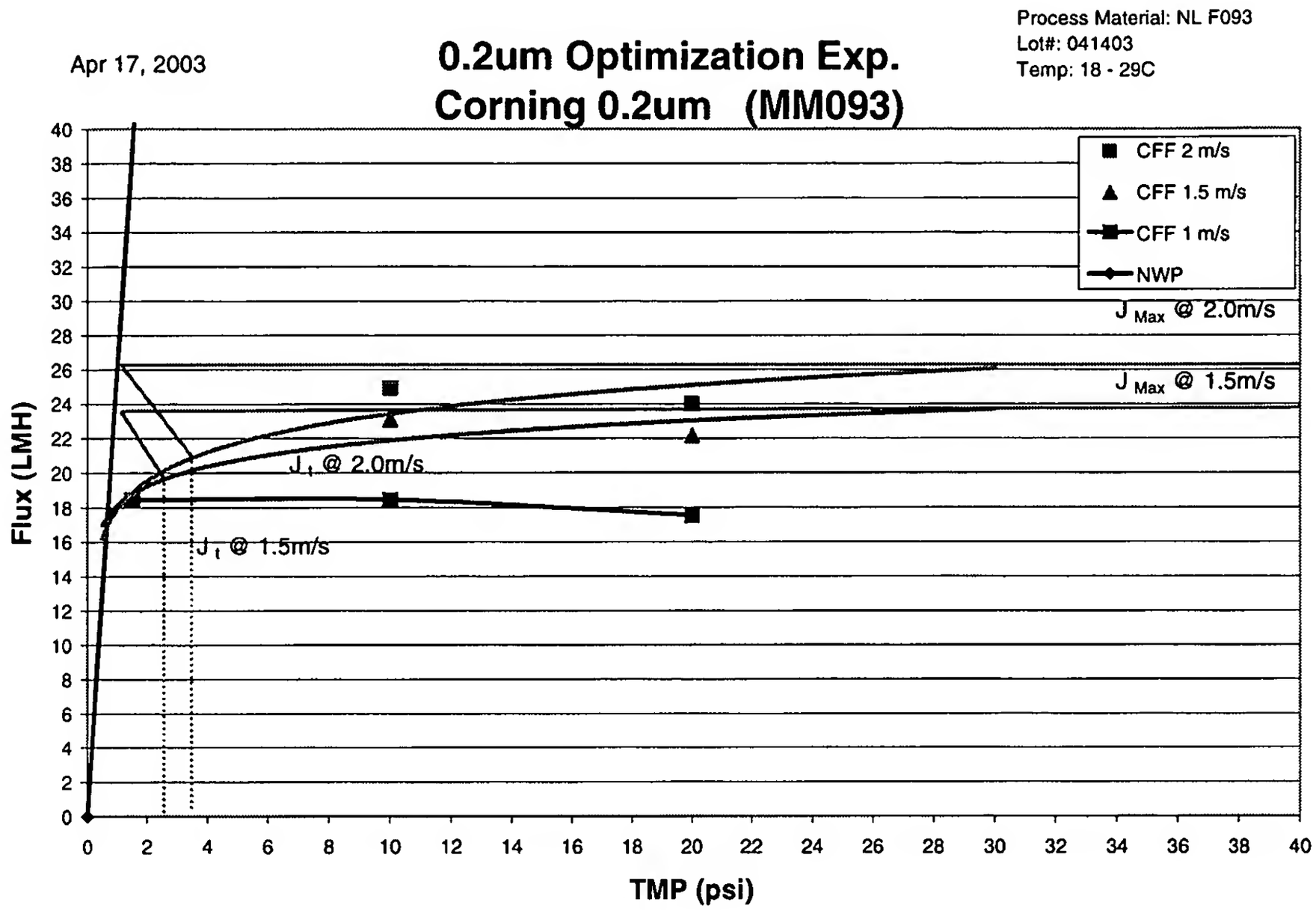
Example #4



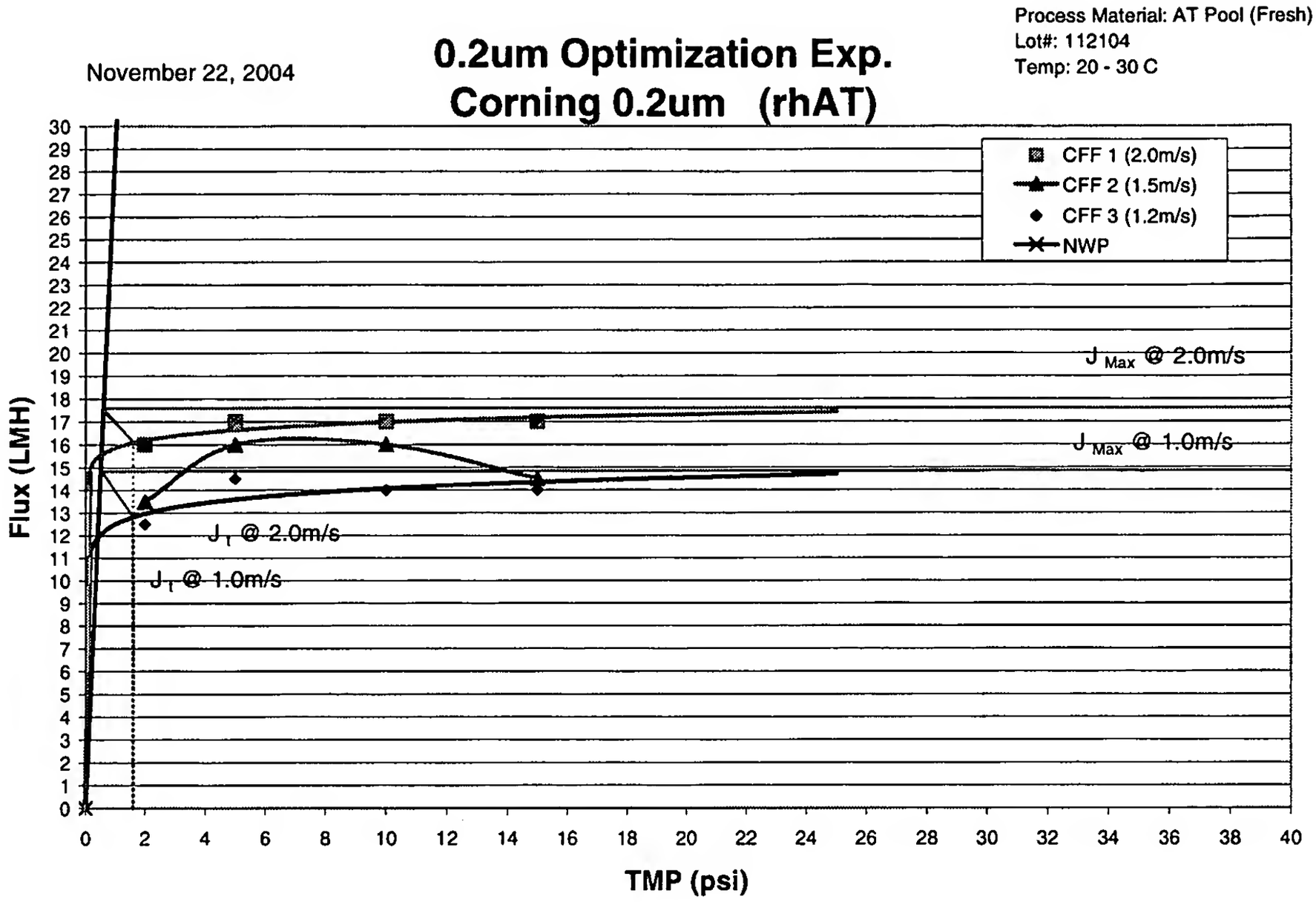
Example #5


Process Material: AT Pool (Fresh)
Lot#: 112104
Temp: 20 - 30 C
November 22, 2004
0.2um Optimization Exp.
Corning 0.2um (rhAT)
CFF 1 (2.0m/s)
CFF 2 (1.5m/s)
CFF 3 (1.2m/s)
NWP
J Max @ 2.0m/s
J Max @ 1.0m/s
J t @ 2.0m/s
J t @ 1.0m/s
Flux (LMH)
TMP (psi)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40

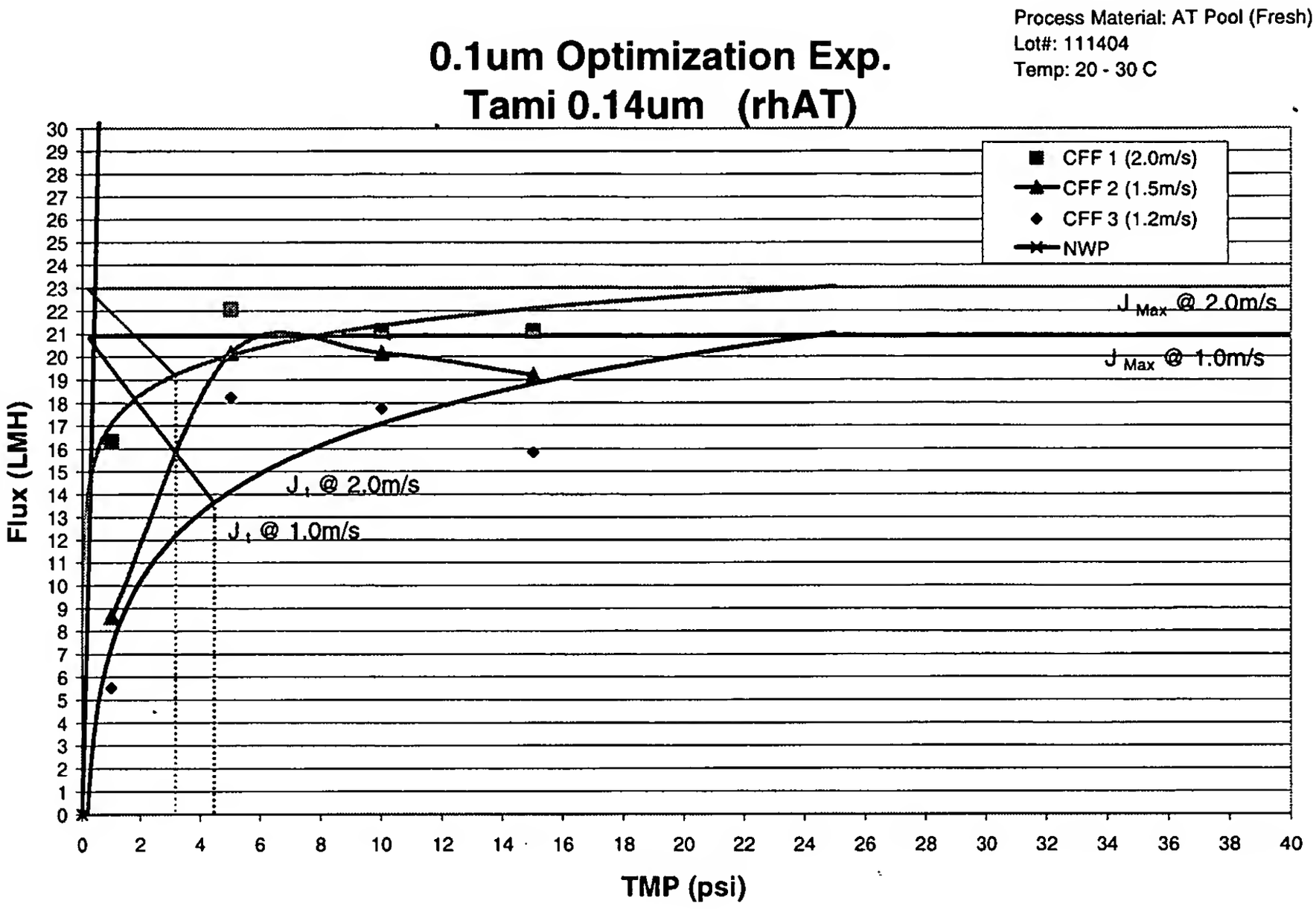
Example #6


Apr 17, 2003
0.2um Optimization Exp.
Corning 0.2um (MM093)
Process Material: NL F093
Lot#: 041403
Temp: 18 - 29C
CFF 2 m/s
CFF 1.5 m/s
CFF 1 m/s
NWP
J Max @ 2.0m/s
J Max @ 1.5m/s
J t @ 2.0m/s
J t @ 1.5m/s
Flux (LMH)
TMP (psi)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40

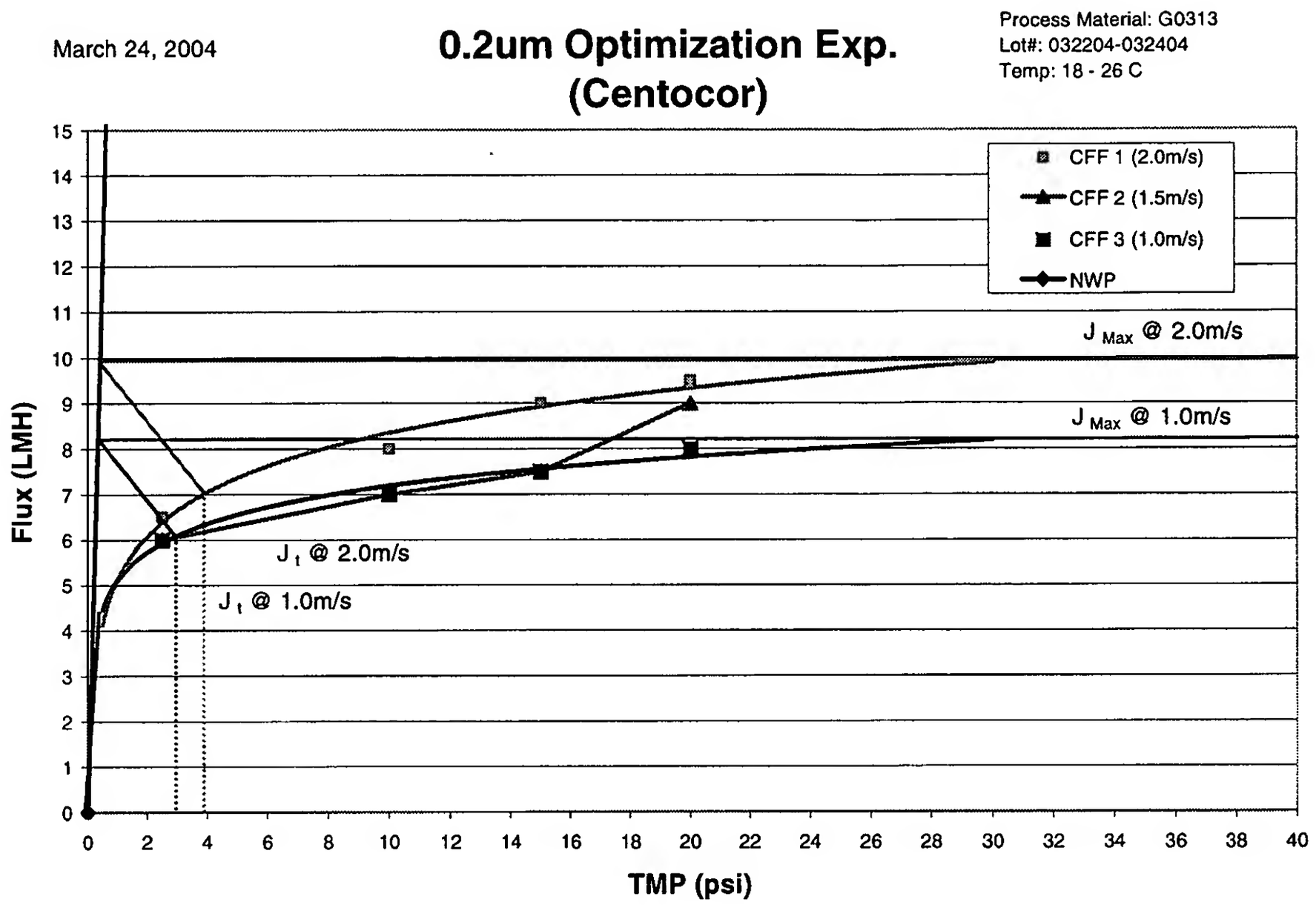
Example #7


Process Material: AT Pool (Fresh)
Lot#: 112104
Temp: 20 - 30 C
November 22, 2004
0.2um Optimization Exp.
Corning 0.2um (rhAT)
CFF 1 (2.0m/s)
CFF 2 (1.5m/s)
CFF 3 (1.2m/s)
NWP
J Max @ 2.0m/s
J Max @ 1.0m/s
J t @ 2.0m/s
J t @ 1.0m/s
Flux (LMH)
TMP (psi)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40

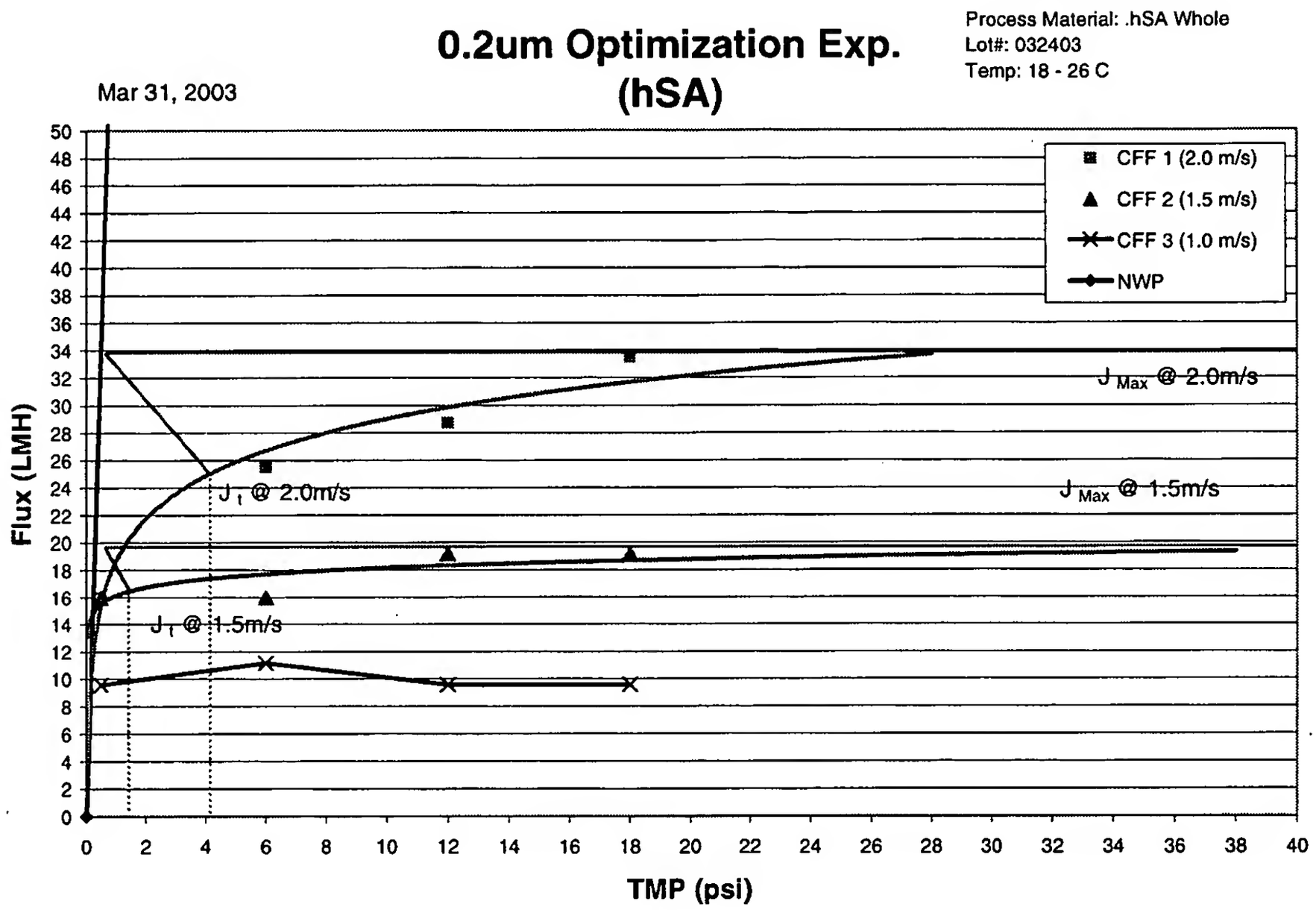
Example #8


0.1um Optimization Exp.
Tami 0.14um (rhAT)
Process Material: AT Pool (Fresh)
Lot#: 111404
Temp: 20 - 30 C
CFF 1 (2.0m/s)
CFF 2 (1.5m/s)
CFF 3 (1.2m/s)
NWP
J Max @ 2.0m/s
J Max @ 1.0m/s
J1 @ 2.0m/s
J1 @ 1.0m/s
Flux (LMH)
TMP (psi)

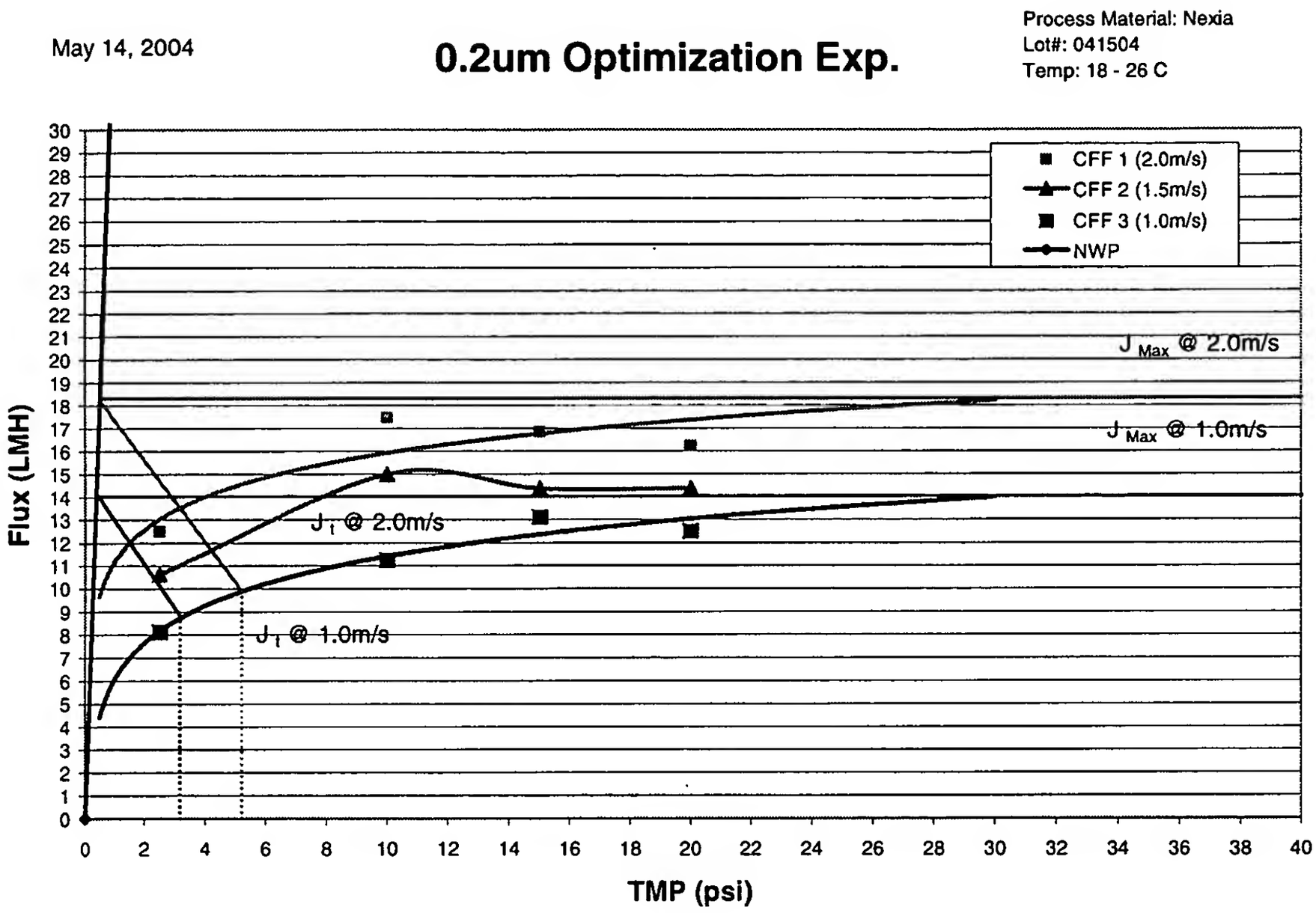
Example #9


March 24, 2004
0.2um Optimization Exp.
(Centocor)
Process Material: G0313
Lot#: 032204-032404
Temp: 18 - 26 C
CFF 1 (2.0m/s)
CFF 2 (1.5m/s)
CFF 3 (1.0m/s)
NWP
J Max @ 2.0m/s
J Max @ 1.0m/s
J t @ 2.0m/s
J t @ 1.0m/s
Flux (LMH)
TMP (psi)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40

Example #10


0.2um Optimization Exp.
(hSA)
Mar 31, 2003
Process Material: .hSA Whole
Lot#: 032403
Temp: 18 - 26 C
CFF 1 (2.0 m/s)
CFF 2 (1.5 m/s)
CFF 3 (1.0 m/s)
NWP
J Max @ 2.0m/s
J Max @ 1.5m/s
J t @ 2.0m/s
J t @ 1.5m/s
Flux (LMH)
TMP (psi)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
48
50

Example #11



Milk is a Unique Feedstream

As previously stated, milk chemistry and composition is a very unique and different starting material from a separation and filtration point of view. Milk is a highly complex and fragile mixture of fat and proteins in water with more than 200 recognized constituents (see Blanc, 1981). Moreover, the number of recognized constituents continues to steadily increase as analytic techniques have been improved. The structure and composition of fat globules, casein micelles in gel networks, nano-droplet dispersions, globular proteins, and lipoprotein particles have the malleability to allow them to be made into hundreds of butter, cream, yogurt, and cheese products. It is comprised of > 6% solids and contains high levels of protein (~ 70 grams per liter) as well as many different kinds of fat. Fat globules and Casein Micelles are both greater than micron sized particles that cause issues in milk filtration and cleaning. In addition, calcium, phosphate and many other minerals are found in milk that makes the overall chemistry quite complex. These properties of milk make it an incredibly complex chemical composition and its

properties are the kinds that chemists and physicists are now only beginning to recognize or understand. Therefore, the development, use, processing and purification of a desired exogenous protein out of the lactation products of such modified animals is an extremely complex undertaking, not addressed or understood by van Reis or other prior art in the field. Added to this complexity is the need to insure that said exogenous protein remains or can be made biologically active. In the present invention the Applicants found methods to accomplish this task.

As previously pointed out amended claim 1 recites several elements not present or suggested in any of the teachings of Van Reis, with amendment these have grown to include:

a) usage of milk as a feedstream;
b) primary usage of ultrafiltration as opposed to microfiltration;
c) operates different flux level/pressure;
d) different pressure variances: and,
e) operates in a different range and under very different parameters.

None of the elements a-e are disclosed in the van Reis reference. Therefore, it is respectfully proposed that the rejection of claim 1 for anticipation by the Van Reis reference is overcome either as an anticipatory reference or one that can provide a basis for an obviousness rejection.

The Rejections Under 35 U.S.C. §112, second paragraph

Pursuant to phone conversations with Examiner Mondesi it is Applicant's position that other than concerns for support in the original specification for an operating range outside of that suggested by van Reis there were a series of rejections based on §112, second paragraph issues. Specifically these were cited as references to: improper antecedent basis; improper dependency; and, recitation of RNA & DNA when the specification recited protein or transgenic protein. With regard to these changes, Applicants are open for an Examiner's amendment to "fix" these

minor objections as to form. In addition, with regard to recitation to DNA & RNA, Applicants specifically agree to amend any claims by way of Examiner's amendment to remove such substantive references.

Applicants invite the Examiner to present any specific issues with regard to §112, second paragraph, not addressed herein directly to them through a telephonic interview or fax and they can be resolved quickly *via* Examiner's amendment

Applicant is not aware of any fees associated with this Response to the Notice of Withdrawal. However, the Commissioner is authorized to charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 9/16/05

By: _____

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